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Figure 2 shows the structures of neoglycopeptide YEE(ahGalNAc)$_3$ (**5**) (**Figure 2a**); oligo-MP U^{m}pT$_7$ (**6**), and 5'-ethylenediamine capped U^{m}pT$_7$ (**6b**) (**Figure 2b**); Structure of the Tracer, 3' conjugate (**Figure 2c**); Reaction scheme for the automated synthesis of SEQ ID NO.:32 with 5'-thiol modifier (**Figure 2d**); and Reaction scheme for the synthesis of **1c** comprising SEQ ID NO.:32 (**Figure 2e**).

Please replace the paragraph on page 12, lines 10-11, with the following:

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Figure 5 illustrates the structures of the [^{35}S]3'-End Labeled hepatitis B virus (HBV) neoglycoconjugates (NG1 is SEQ ID NO.:27; NG2 is SEQ ID NO.:28; NG3 is SEQ ID NO.:29; NG4 is SEQ ID NO.:30).

Please replace the text on page 22, line 33, with the following:

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TGCTCATGGTGCACGGTCTACGA (SEQ ID NO.:8)

Please replace Table 5, the entire text of page 40, with the following:

Table 5. Oligonucleotide Alternating Methylphosphonate Analogs.

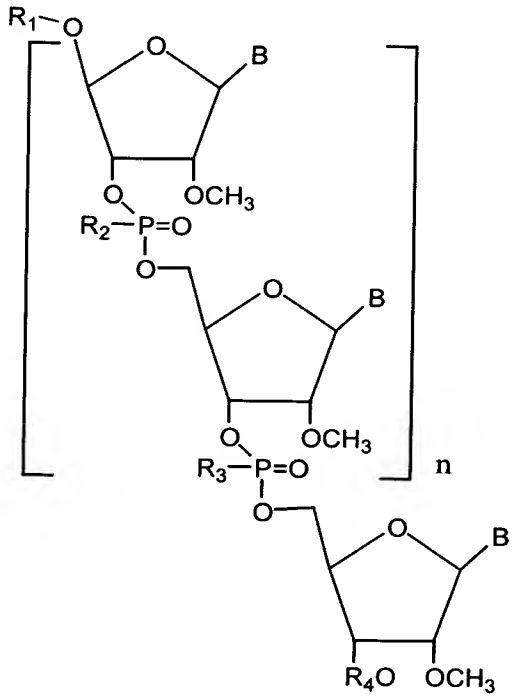
Sequence

1 (n=7) ApGpUpCpApGpUpCpApGpUpCpApGpU (SEQ ID NO.:24)

2 (n=7) GpUpUpCpUpCpCpApUpGpUpUpCpApG (SEQ ID NO.:25)

3 (n=10) UpUpUpApUpApApGpGpGpUpCpGpApUpGpUpCpCpApU (SEQ ID NO.:26)

where p: phosphodiester linkage
p: methylphosphonate linkage
ps: phosphorothioate linkage



Oligonucleotide	R_1	R_2	R_3	R_4
a	H	O^-	CH_3	3'-conjugate
b	C6-thiol-ps	O^-	CH_3	3'-conjugate
c	5'-conjugate	O^-	CH_3	3'-conjugate
d	Ligand-SMCC-AET	O^-	CH_3	H
e	EDA	O^-	CH_3	H

where Ligand: YEE(ah-GalNAc)$_3$
5'-conjugate: YEE(ah-GalNAc)$_3$-SMCC-S$(CH_2)_6$-ps linkage (Figure 3)
3'-conjugate: Tracer Unit (Figure 9)
EDA: ethylenediamine

Please replace the paragraph on page 47, lines 2-21, with the following:

The purified disulfide-containing oligomers were then used in conjugation with SMCC-YEE(ah-GalNAc)$_3$ similarly as described in Example 2. Most conjugation reactions were performed by using 1.5-2 equivalents of SMCC-YEE(ah-GalNAc)$_3$ to the thiol oligomers. These resulted in quantitative conjugation of the oligomers in all of the reactions performed. Excess ligand and buffer salts were easily removed by a G-25 column, eluting with 20% ethanol, to give highly pure conjugates. Conjugation reactions were also performed using excess amount of thiol oligomers instead, e.g., 1.5 equivalent of the thiol oligomers to the ligand. In these cases, all of the ligands were consumed in the reactions and the remaining excess amount of thiol-oligomers were removed by preparative reversed phase high pressure liquid chromatagraphy (HPLC). Following are the sequences of four oligodeoxyribonucleoside phosphorothioate A-L-P conjugates synthesized by the above method (**Figure 5**). NG1: YEE(ahGalNAc)$_3$-SMCC-5'GTTCTCCATGTTCAG3' (SEQ ID NO.:27), which targeted the HBV sa-gene, NG2: YEE(ahGalNAc)$_3$-SMCC-5'TTTATAAGGGTCGATGTCCAT3' (SEQ ID NO.:28), which targeted the HBV c-gene, NG3: YEE(ahGalNAc)$_3$-SMCC-5'AAAGCCACCCAAGGCA3' (SEQ ID NO.:29), which targeted the HBV e-site, and the random controls, NG4: YEE(ahGalNAc)$_3$-SMCC-5'TGAGCTATGCACATTCAGATTT3' (SEQ ID NO.:30), and NG5: YEE(ahGalNAc)$_3$-SMCC- 5'TCCAATTAGATCAG3' (SEQ ID NO.:31).

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Please replace the paragraph starting on page 55, line 9, and ending on page 56, line 6, with the following:

The above examples illustrate that OMNP's can be conjugated to the hepatic specific ligand YEE(ah GalNAc)$_3$ to yield a homogeneous and defined neoglycoconjugate. Furthermore, this neoglycoconjugate is taken up by hepatoma-derived cells (Hep G2) specifically and at an enhanced rate in vitro. The above results have been extended to consider oligonucleotides with other nuclease resistant backbone modifications, such as phosphorothioates (ps) oligomers comprised of 2'Omethyl ribose moieties and alternating phospho-diester/methylphosphonate linkages (2'Ome-po/mp). The experimental methods were identical to those utilized in Examples 4 and 5. Results of these experiments were very similar to those observed with the OMNP containing neoglyco-conjugates. Neoglycoconjugate containing phosphorothiate oligomers were synthesized according to

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Conjugate Method 2. YEE (ahGalNAc)$_3$-SMCC-ps $^{5'}$GTTCTCCATGTTCAG$^{3'}$ (NG-1) (SEQ ID NO.:27) was labeled with ^{35}S using the 3'-end labeling method described in Conjugation Method 2 displayed a linear uptake to the extent of 17.25 pmoles/10^6 cells at 24 hours. In contrast the corresponding unconjugated oligomer ps $^{5'}$GTTCTCCATGTTCAG$^{3'}$ (SEQ ID NO.:27) was taken up by Hep G2 cells at a diminished rate, reaching 1.01 pmoles/10^6 cells at 24 hours. In a similar fashion, neoglyco-conjugates containing 2' OMe alternating po/mp oligomers (YEE(ahGalNAc)$_3$-SMCC-2'OMe $^{5'}$AG$_p$UC$_p$AG$_p$UC$_p$AG$_p$UC$_p$AG$_p$U$^{3'}$) (SEQ ID NO.:32) displayed a linear uptake to the extent of 24.3 pmoles/10^6 cells at 24 hours. The corresponding unconjugated oligomer (2'OMe $^{5'}$AG$_p$UC$_p$AG$_p$UC$_p$AG$_p$UC$_p$AG$_p$U$^{3'}$) (SEQ ID NO.:32) displayed minimal uptake of less than 1 pmole/10^6 cells at all time points assayed. All oligomers and neoglycoconjugates were stable in cell culture media up to 24 hours. These results illustrate the delivery utility of the unique ligand-linker complex and give us a platform to expand this system to the delivery of other therapeutic agents.

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Please replace the paragraph starting on page 56, line 27, and ending on page 57, line 16, with the following:

The cellular uptake experiments described utilizing ^{32}P-labeled oligo-mp conjugates were extended to examine the cellular association of neoglycoconjugates comprised of neoglycopeptide **5** and oligomers of other nuclease resistant backbones, most notably ps and 2'OMe po/mp, with Hep G2 cells. Neoglycoconjugates containing phosphorothioate oligomer, YEE(ahGalNAc)$_3$-SMCC-ps $^{5'}$GTTCTCCATGTTCAG$^{3'}$ (NG-1) (SEQ ID NO.:27) was labeled using Conjugation Method 2, which displayed linear uptake to the extent of 17.25 pmoles/10^6 cells at 24 hours. In contrast, the corresponding unconjugated oligomer ps $^{5'}$GTTCTCCATGTTCA-G$^{3'}$ (SEQ ID NO.:27) was taken up by Hep G2 cells at a diminished rate, reaching 1.01 pmoles/10^6 cells at 24 hours. In a similar fashion, neoglyco-conjugates containing 2'OMe alternating po/mp oligomers (YEE(ahGalNAc)$_3$-SMCC-2'OMe $^{5'}$AG$_p$UC$_p$AG$_p$UC$_p$AG$_p$UC$_p$AG$_p$U$^{3'}$) (SEQ ID NO.:32) displayed a linear uptake to the extent of 28.52 pmoles/10^6 cells at 24 hours (**Figure 9**; Table 6). The corresponding unconjugated oligomer (2'OMe $^{5'}$AG$_p$UC$_p$AG$_p$UC$_p$AG$_p$UC$_p$AG$_p$U$^{3'}$) (SEQ ID NO.:32) displayed minimal uptake of less than 1 pmole/10^6 cells. These results illustrate the delivery utility of the unique

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ligand-linker complex and allow a platform to expand this system to the delivery of other therapeutic agents.

Please replace Table 6, page 59, with the following:

TABLE 6-Uptake of conjugated YEE(ah-GAlNac)$_3$-SMCC-AET-2'O-Me $^{5'}AG_PUC_PAG_PUC_PAG_PUC_PAG_PU^{3'}$ (SEQ ID NO.:24) (1d) and EDA-2'-O-Me-$^{5'}AG_PUC_PAG_PUC_PAG_PUC_PAG_PU^{3'}$ (SEQ ID NO.:32) (1e) by Hep 2G 2.2.15 cells in culture (pmoles/10^6 cells)

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OLIGOMER	1 HOUR	2 HOURS	3 HOURS	24 HOURS
1d	3.63	7.71	14.16	28.52
1e	0.277	0.305	0.400	0.450

Please replace Table 7, page 59, with the following:

TABLE 7-Uptake of YEE(ah-GAlNac)$_3$-SMCC-S$(CH_2)_6$-*ps*- 2'O-Me-$^{5'}AG_PUC_PAG_PUC_PAG_PUC_PAG_PU^{3'}$ (SEQ ID NO.:32) $-U^MDt^{*3'-3'}$ (dt-T)-^{32}P-EDA (1c) by Hep G2 2.2.15 cells in culture (pmoles/10^6) cells

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OLIGOMER	4 HOURS	8 HOURS	12 HOURS	16 HOURS	24 HOURS
1c	9.44	18.60	22.05	24.92	28.97

Please replace the paragraph on page 64, lines 4-22, with the following:

Male CD-1 mice were injected as described in Example 9 with 30 pmoles of the neoglycoconjugate YEE(ahGalNAc)$_3$-SMCC-ps-(TTTATAAGGGTCGATGTCCAT)-$^{\{35S\}}$(psA)$_n$ (SEQ ID NO.:28) labeled utilizing the 3'-end labeling method as described in Conjugation Method 2. For comparison, a conjugate which lacks the three terminal GalNAc residues, YEE(ah)$_3$-SMCC-ps-(TTTATAAGGGTCGATGTCCAT)-(psA)$_n$ $^{\{35S\}}$ (SEQ ID NO.:28) was also synthesized. This sugarless conjugate served as a control for the study of ligand (GalNAc)-specific uptake in mice. Experimental results were very similar to those observed in Example 10. The conjugate containing the terminal sugar residues associated to the greatest extent with the liver, reaching a value of 46.19 % of the injected dose 15 minutes post-injection. The ranking of total radioactivity in the other tissues measured at 15 minutes post-injection was, in decreasing order: muscle > blood > kidney >spleen. The peak value of

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radioactivity for the urine was 4.51% of the injected dose and was reached after 15 minutes. The amount of radioactivity associated with the kidneys and blood decreased over time.

Please replace the paragraph on page 70, lines 18- 28, with the following:

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A tritium labeled 12 mer (d-Tp*TCCTCCTGCGG) (SEQ ID NO.:33) consisting of all methylphosphonate backbone except the last 5' terminal phosphodiester linkage was injected i.v. in a single dose in mice. Organs were collected in 2, 5, 10, 30, 60 and 120 minutes after drug administration. The data shows that the radioactivity was not allocated in liver, lung, muscle or spleen, and was rapidly disappearing from the plasma into the kidney and urine. The HPLC study showed that the intact 12-mer was metabolized to 11-mer via enzymatic cleavage of the terminal nucleotide and both were eliminated rapidly into the urine after i.v. injection. Thus, the results reported herein agree well with the results obtained earlier, demonstrating the importance of the GalNAc terminal in directing the uptake of oligomer conjugate into liver.

Please replace the paragraph on page 75, lines 9-24, with the following:

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Methods: The three therapeutic neoglycoconjugates utilized in this study were synthesized by conjugation of the following ps-oligomers, previously shown to inhibit HBV replication in vitro (Korba and Gerin, 1995, supra), to the liver specific ligand YEE(ahGalNAc)$_3$: (1) 5'GTTCTCCATGTTCAG3' (SEQ ID NO.:27) which targets the translation initiation site of the surface antigen gene (sa-gene), (2) 5'TTTATAAGGGTCGATGTCCAT3' (SEQ ID NO.:28) which targets the translational initiation site of the core gene (c-gene) and overlaps the HBV polyadenylation site and (3) 5'AAAGCCACCCAAGGCA3' (SEQ ID NO.:29) which targets the unpaired loop of the encapsidation site of the HBV pregenome (e-site). The base sequence used to synthesize the oligomers for this study was a HBV subtype ayw (Galibert, *et.al.*, (1979), *Nature* (London), 281:646-650), the same subtype expressed in vitro by HepG2 2.2.15 (Acs et al., (1987), *Proc. Natl. Acad. Sci.*, 84:4641-4644. In addition, two additional ps-oligomers, which are non-complementary to the HBV genome, NG4: $^{5'}$TGAGCTATGCACATTCAGATTT$^{3'}$ (SEQ ID NO.:30) and NG5: $^{5'}$TCCAATTAGATCAG$^{3'}$ (SEQ ID NO.:31), were prepared as controls to assay for non-specific effects of the ps-neoglycoconjugates.